REMARKS/ARGUMENTS

I. Status of the Claims

Claims 62, 68, and 69 are pending in the present application. Claims 63-67 have been canceled because they are directed to *specific* embodiments which may not have adequate support. Applicants reserve the right to file one or more applications directed to this canceled subject matter. Claim 62 has been amended to recite that the vector contains a transcriptional regulatory sequence and that gene activation is caused by the transcriptional regulatory sequence. Support for gene activation by a transcriptional regulatory sequence on a vector is found, *inter alia*, in the Abstract. Claim 62 is amended to recite that the "said one or more cells" in step (c) refers to the cells of step (b) that are cultured so as to allow gene activation. New claim 70 is sought to be entered. The claim recites that the compound is tested against purified protein. Support can be found, *inter alia*, in the specification on page 7, lines 28-30. No new matter has been added.

II. Telephonic Interview

An interview was held on May 16, 2003, with Examiner Ram Shukla, Supervisory Examiner Deborah Reynolds, Applicants' attorney Anne Brown, and Dr. Youssef Bennani, Director of Medicinal Chemistry at Athersys, Inc.. Mr. Brian Stanton also participated for the final quarter hour of the interview. The contents of the interview are discussed in more detail in Applicants' remarks herein.

III. Miscellaneous

A. Priority

The Examiner indicates that priority has been assigned to the filing date of the application 09/276,820, filed March 26, 1999. The Examiner appears to take the position that this application describes the invention as claimed. He asserts that the first priority application, U.S. Application Number 08/941,223, does not disclose the invention because "none of the indicated pages recite a drug discovery method as instantly claimed". Office Action, page 2. He assigns a priority date for the claims to 09/276,820.

Applicants disagree that the invention as claimed is not disclosed in 08/941,223 (1) for reasons given in Applicants' Response filed April 25, 2002, and in the Declaration of Dr. Youssef Bennani, submitted with that Response, (2) the discussion in this present Response, and (3) the comments of Dr. Dale Dhanoa, Senior Vice President, Research and Discovery, Predix Pharmaceuticals, in the Declaration attached to this Response.

B. Specification

Applicants include a shortened Abstract as requested by the Examiner on page 2 of the Office Action.

IV. The Rejections

A. Rejection of Claims 62-68 under 35 U.S.C. § 112, First Paragraph

On page 2 of the Office Action, claims 62-68 remain rejected under 35 U.S.C. §112, first paragraph, on the grounds that the specification does not describe the claims so as to reasonably convey to one skilled in the art that the inventor had possession of the invention. Applicants respectfully traverse the rejection.

The Written Rationale for the Rejection

The Examiner indicates that the claims are rejected for the reasons set forth in the Examiner's Office Action dated October 25, 2001. In that Office Action the Examiner stated that the specification does not set forth the *structure* of the compounds, a *representative number* of compounds, or *features* of the compounds to be used in compound testing. The Examiner concludes, therefore, that the claims are not adequately described.

In the Final Office Action, the Examiner writes:

> It is emphasized that the only description/reference to a drug in the specification is lines 28-30 on page 11 continued in lines 1-2 on page 12. Applicants have not provided any description of compounds that will be used in the assay.
>
> Therefore, the written description is maintained [sic] for reasons of record.

The Expert Declaration is Sufficient

In response to this position, the Applicants previously submitted a Declaration from Dr. Youssef Bennani, Director of Medicinal Chemistry at Athersys, Inc.. Dr. Bennani explained that the compounds themselves would not be important up-front for drug testing because compounds were routinely selected at random from compound libraries.

The Examiner dismisses the Declaration as follows.

> In the Declaration, Dr. Bennani has stated that in view of his experience, structure of compounds is not important, however, Applicants' arguments are not evidence. [sic] In other words, Applicants have provided any evidence [sic] of record that indicates that structure of compounds is irrelevant in drug discovery assay.

The Declaration is not "Applicants' arguments". Dr. Bennani's factual statement itself constitutes evidence. The Examiner has, therefore, impermissibly disregarded a factual statement of a qualified expert. A Declaration by a qualified party regarding what is and is not used for compound testing is proper evidence per se. The statements by Dr. Bennani are based on his experience of scientific procedure in the relevant field of drug discovery. Dr. Bennani has explained that because compounds are selected at random, there is no limitation on the structure. The Examiner has presented no reason to challenge this conclusion. If the Examiner believes that there is scientific reason to challenge this factual statement, it is incumbent upon the Examiner to present this reason. The Examiner does not state his reason. Accordingly, Dr. Bennani's declaratory evidence has been improperly disregarded.

The Written Rejection Does Not Comport with Patent Office Policy

In response to this rejection, Applicants also submitted a slide presentation from Mr. Brian Stanton setting forth the position of the U.S. Patent and Trademark Office on written description of generic claims for methods of *screening* – as opposed to methods of *using* – test compounds. The policy of the Patent Office has been, and currently is, that adequate support for claims generically directed to drug screening does not require disclosure of compounds. This point was discussed in the interview with Mr. Stanton. Mr. Stanton indicated that if the claims were generic drug discovery claims, which they are, then compounds need not be described. Mr. Stanton indicated that he would review these claims and discuss the issue with the Examiners.

Patent Office Policy is Demonstrated in the Cited Patent

In the previous Response, Applicants responded to the Examiner's citation of U.S. Patent No. 6,159,705. They pointed out that while claim 1 in the '705 patent is generically directed to methods for *screening* test compounds, no genus of test compounds is described. Yet the claim issued. This issuance is consistent with the policy discussed by Mr. Stanton in the interview regarding generic drug screening claims.

In the Final Office Action, the Examiner took the position that the '705 patent is not relevant "because the cited patent describes assay for compounds relating to a certain receptor and a certain cell type and based on the structure of the peptides the written description

requirement is met". Applicants disagree. The claim encompasses *any and all compounds, regardless of structure*. The disclosure only discloses a few peptides.

Claim 1 is not limited to an assay for identifying peptides. It recites "an assay for identifying *a compound* that modulates a heterologous receptor...by contacting the yeast cell with a test *compound*; and detecting an alteration in a signal produced by the endogenous yeast gene; to thereby identify *a compound* that modulates the heterologous receptor". (Italics added.) Therefore, it encompasses any and all compounds, including small molecules, peptides, anti-sense RNA, small interfering RNA, and the like. In the Office Action, the Applicants' claims are rejected because "a representative number of compounds" was not disclosed. The '705 patent specification describes a few peptides, not a representative number of compounds. Accordingly, Applicants submit that the claim in the '705 patent is relevant to the rejection of Applicants' claims, inconsistent with the rejection in the Office Action, and consistent with Mr. Stanton's position.

Verbally-Stated Rationale for Rejection

As discussed above, the only basis for this rejection in both of the Office Actions is that the *compounds* used in drug screening are not adequately described.

New Rationale for Rejection

In the interview, however, Examiner Deborah Reynolds indicated that the rationale for the rejection was not insufficient description of compounds. Examiner Reynolds took the position that the specification does not describe the claim as a whole, i.e., the combination of steps (a)-(c) with steps (d)-(e). In the interview, Examiner Reynolds addressed the specific disclosure of drug discovery in the specification and took the position that ANY disclosure of using the RAGE technology for compound testing was limited to testing a compound against a purified protein, not a cell.

This is a different rationale from that set forth in both Office Actions. See pages 2 and 3 of the Final Office Action. The Office Action was clear that the rejection was based on the position that the application failed to adequately disclose compounds. Procedurally, therefore, a new non-final Office Action should be issued. Nevertheless, to expedite prosecution, Applicants have addressed the new position with a Declaration of a third party with expertise in the field of drug discovery. The party has reviewed the specification and commented on whether the specification would have reasonably conveyed to the person of ordinary skill in the art that Applicants had possession of an invention in which cells expressing activated genes were screened against a test compound (i.e., combine steps (a)-(c) with steps (d)-(e)).

New Third Party Declaration

The Examiner is directed to the attached Declaration of Dale Dhanoa, Ph.D., Senior Vice President Research and Discovery, Predix Pharmaceuticals. In the Declaration, Dr. Dhanoa comments on what he thought was described in Applicants' application with respect to drug discovery in the context of the disclosed activation technology. Dr. Dhanoa states that the drug discovery process would involve, at a minimum, screening a test compound for its effect. He indicates that typically two approaches were commonly used to assess the end point. These included protein-based screening and cell-based screening. He states that although *in vitro* screening of a test compound against a protein outside of the cell was used, a whole cell assay was actually a better measure of the performance of test compounds when one tested for the effect of the compound on a cellular process. He states that, in fact, screening compounds in cell-based assays was a more efficient process. He states that what the specification describes to him was that cells can be cultured *in vitro* and cells that express an activated gene can be used in the drug discovery process. This means that the whole cell would be exposed to a test compound and the effect of the compound would be assessed. Dr. Dhanoa also states that he believes, as an expert, he is qualified to speak to what the person of ordinary skill in the field would have realized to be described in the application, namely to expose a test compound to a gene product, both *in vitro* and in a whole cell assay. Accordingly, he concluded that a person of ordinary skill in the field of drug discovery, reading the application, would have realized that the Applicants, by disclosing the drug discovery process, were, in fact, describing the claimed method.

Dr. Dhanoa refers to disclosure in 08/941,223. This is the earliest priority application. For the Examiner's convenience, Applicants point out the same disclosure in the present application, 09/484,331: 7:25-30; 11:27-30; 12:1-2; 32:3-6; 35:26-30; 69:14-18.

Based on the Declaration discussed above, Applicants believe that the new grounds for rejection have been addressed and the rejection on these grounds overcome. Reconsideration and withdrawal of the rejection of the claims as lacking adequate written description is, therefore, respectfully requested.

B. Rejection of Claims 62-68 under 35 U.S.C.§ 112, First Paragraph

On page 3 of the Office Action, claims 62-68 are remain rejected under 35 U.S.C.§ 112, first paragraph, on the grounds that these claims are not enabled. Applicants respectfully traverse the rejection.

First the Examiner takes the position that this specification is only enabled for vectors that are able to transcriptionally activate a gene. Accordingly, the claims have been amended to recite that the vector contains a transcriptional regulatory sequence that activates expression.

On page 4 of the Office Action, the Examiner also rejects the claims as follows:

> ...the person of ordinary skill would not be able to determine whether a compound that was isolated by the claimed screening method would have any of the properties of a drug. It is noted that the claimed method is a drug discovery method, not just screening for a compound.

This point was discussed in the interview.

Applicants pointed out that the claim is directed to screening a test compound, not to screening a "drug". The preamble mentions that the claim is generally directed to a method for drug discovery. The claimed steps are part of the drug discovery process. But these steps do not require an actual drug. They merely require a test compound. Step (d) recites that the cell is treated with "one or more test compounds". Step (e) recites that the method involves determining the ability of "one or more test compounds" to interact with a product of a desired gene or affect a desired phenotype.

In the interview, Examiner Reynolds explained that lack of enablement arises because there is inadequate written description for drug discovery with cells. As discussed above, Examiner Reynolds took the position that the specification, at best, relates to exposing a *purified* protein to a test compound. Therefore, overcoming the rejection based on inadequate written description should also serve to overcome the enablement rejection.

Finally, Applicants address the grounds of rejection in the paragraph spanning pages 5 and 6 of the Final Office Action. Here it is stated that the instant issue is "that even when a cell in which a desired gene is activated, there is no way of knowing if the desired phenotype observed in a selected cell is due to the activated expression of only the desired gene or due to an activation of multiple genes". Examiner Reynolds pointed out that this point of argument, again, relates to inadequate description for a method of compound testing against cells. She again stated her belief that the specification shows that, at best, only purified proteins are subjected to

drug discovery. Her position was that, even if steps (d) and (e) are inherent in the term "drug discovery", there is no disclosure of applying the method to cells. She repeated that this is the real basis of the enablement rejection. Examiner Reynolds indicated that what the Examiner had intended to set forth in the Office Action was that the combination of steps (a), (b) and (c) with steps (d) and (e) would not have been readily envisaged because the specification lacks disclosure for drug screening with RAGE activated cells.

The issue of adequate description for this aspect has been addressed by the attached Declaration. With resolution of the issue and the claim amendment, Applicants believe that all of the grounds for this rejection have been addressed and the rejection overcome.

C. Rejection of Claims 62-68 under 35 U.S.C.§ 112, Second Paragraph

On page 6 of the Office Action, claims 62-68 remain rejected under 35 U.S.C. § 112, second paragraph, on the grounds that they are indefinite and fail to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Applicants respectfully traverse the rejection.

Claim 62 is rejected on the grounds that "said one or more cells" in step (c) lacks clear antecedent basis. Accordingly, the claim now recites that the cells are from step (b).

On page 7 of the Office Action, the Examiner maintains the rejection on the grounds that claims 62 and 63 are incomplete for "omitting essential steps".

In the interview, Applicants discussed the two steps alleged to be essential and omitted. (1) exposing the compound to a cell in which the gene is not activated in addition to testing the compound against a cell where the gene is activated. Dr. Bennani explained that this step is unnecessary and extremely impractical. If a large number (eg, a million) of compounds is tested, a large number (i.e., a million) of extra steps will be required. These extra steps essentially provide no useful information. He explained that since the compound is being tested against an activated gene (i.e., for its effect on that gene) there is no reason to expose the compound to a cell that does not even express this gene. The Examiners accepted this argument.

(2) comparing the cell with the activated gene to the parent cell without the activated gene. Dr. Bennani pointed out that this was inherent in step (c) of the claim. The Examiners accepted this.

However, Examiner Shukla indicated that what he meant was that there should be a step for comparing the result obtained by exposing an activated cell to a test compound against the result obtained from an activated cell not exposed to the test compound. This was a point of argument found in the rejection of claim 62 under 35 U.S.C. § 112, first paragraph. See page 9, Office Action dated October 25, 2001.

Applicants point out that claim 62 was amended to delete the limitation in which the effect of the compound on a desired phenotype is determined. The claim now only recites the ability of a test compound to *interact* with the gene product. Therefore, no step is necessary

where the interaction of the test compound with an activated gene product is compared to the result in an activated cell not exposed to test compound.

In view of the above discussion, Applicants believe all grounds of rejection to be addressed and the rejection overcome. Reconsideration and withdrawal of the rejection is, therefore, requested.

D. Rejection of Claims 62 and 66 under 35 U.S.C. § 102(e)

On page 7 of the Office Action, claims 62 and 66 have been rejected under 35 U.S.C. § 102(e) on the grounds that they are anticipated by U.S. Patent No. 6,159,705 (herein the '705 patent). Applicants respectfully traverse the rejection.

This point was discussed in the interview. The Examiners were directed to the schematic diagram provided with the Brief Description of Arguments to be Presented. This diagram is included as Appendix A to this Response. Applicants' attorney pointed out that the claims require a step where there is interaction of the test compound with the product of the activated gene. (Step (e).) Applicants' attorney pointed out that the '705 patent only teaches the interaction of a test compound with the receptor and not with the gene that is activated in the cell by integration of the vector. The Examiner pointed out that the receptor was activated and the compound interacted with the receptor. Applicants' attorney pointed out, however, that the claim calls for activation of an endogenous gene by integration of the vector and interaction of the compound with an endogenous gene that is activated because of integration of the vector.

Activation of the receptor in the reference is unrelated to integration of the vector. Therefore the '705 patent does not anticipate the claim. Both Examiners appeared to accept this argument and requested that Applicants restate the argument in their Response.

Accordingly, Applicants believe that the grounds of rejection have been addressed and the rejection overcome.

V. Conclusion

Applicants believe they have addressed all of the grounds of rejection and have overcome all of the rejections. Reconsideration and withdrawal of the rejections is, therefore, respectfully requested.

The rejection of the claims as lacking adequate written description has been overcome by argument. The rejection based on the position that the structure of the test compounds is not disclosed has been overcome by pointing out that the claim is a generic drug screening claim, that compounds are tested from off the shelf, and that it is the policy of the U.S. Patent and Trademark Office that the specification need not disclose the test compounds for a generic claim to drug screening.

On the new rationale that the specification does not describe compound screening using cells, Applicants have presented the Declaration of a qualified third party stating that the person

of ordinary skill in the art would have found such an embodiment to be described by the Applicants' disclosure.

With respect to rejection of claims as not enabled, Applicants have overcome this rejection with argument and amendment. Applicants have amended the claims to recite that the vector contains a transcriptional regulatory sequence. The grounds that the claim is not enabled because the compounds are not been described has been overcome by a third party declaration.

The rejection under 35 U.S.C. § 112, second paragraph, is overcome by argument. The grounds that an essential step is to expose the compound to a cell in which the gene is not activated have been addressed by pointing out that this step is unnecessary and impractical since it provides no useful information.

The grounds that the claims should recite a step wherein the cell with the activated gene would be compared to the parent cell without the activated gene have been addressed by pointing out that this step is inherent in step (c) of the claim.

Regarding the rejection of the claim as anticipated, this rejection has been overcome by argument because the reference discloses a test compound that does not interact with a product of a desired activated gene.

For all these reasons Applicants submit that all grounds of rejection have been addressed and the rejection overcome. Reconsideration and withdrawal of all the rejections is, therefore, respectfully requested.

Accordingly, Applicants believe that the application is in condition for allowance. Early notification in that regard is requested. If the Examiner believes that a telephonic interview would expedite prosecution of this case, he is invited to contact Applicants' attorney, Anne Brown, at 216-426-3586 or Cynthia L. Kanik, at 617-227-7400.

The Commissioner is hereby authorized to charge any fee deficiency to Deposit Account No. **50-2546**, referencing Attorney Docket No. ATX-007CP4DV12.

Respectfully submitted,

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CURRENTLY PENDING CLAIMS
U.S. SERIAL NO. 09/484,331
(ATTORNEY DOCKET NO. 0221-0003L)

Claims 1-61 (cancelled).

Claim 62 (previously amended): A method for drug discovery comprising:

(a) integrating a vector into the genome of one or more eukaryotic cells, wherein said vector integration activates expression of an endogenous gene in said one or more cells;

(b) culturing said one or more cells under conditions favoring expression of said activated gene, thereby producing a gene product of said activated gene;

(c) screening said one or more cells for a cell in which a desired gene is activated or for a cell in which a desired phenotype is induced by said activated gene;

(d) treating said cell, in which said desired gene is activated or in which said desired phenotype is induced, with one or more test compounds to be screened for drug activity; and

(e) determining the ability of said one or more test compounds to interact with a product of said desired activated gene.

Claim 63 (previously added): A method for drug discovery comprising:

(a) integrating a vector into the genome of one or more eukaryotic cells, wherein said vector integration activates expression of an endogenous gene in said one or more cells;

(b) culturing said one or more cells in reduced-serum cell culture medium under conditions favoring production of a protein encoded by said activated gene and secretion of said protein into the cell culture medium;

(c) screening said one or more cells for a cell in which a desired gene is activated and the protein encoded by said desired gene is secreted into the cell culture medium; and

(d) screening one or more test compounds for drug activity by determining the ability of said test compounds to interact with said secreted protein in said cell culture medium.

Clam 64 (previously added): The method of claim 63, further comprising concentrating said cell culture medium prior to said screening in (d).

Claim 65 (previously added): The method of claim 63, further comprising isolating said protein prior to said screening in (d).

Claim 66 (previously added): The method of claim 62 wherein said vector comprises a transcriptional regulatory sequence and wherein expression of said endogenous gene is activated by means of said transcriptional regulatory sequence.

Claim 67 (previously added): The method of claim 63 wherein said vector comprises a transcriptional regulatory sequence and wherein expression of said endogenous gene is activated by means of said transcriptional regulatory sequence.

Claim 68 (previously added): The method of any of claims 62–67 wherein said vector integrates into the genome by non-homologous recombination.

Claim 69 (previously added): A method for drug discovery comprising:

(a) integrating a vector, comprising a promoter, into the genome of one or more eukaryotic cells, by non-homologous recombination, wherein said promoter activates expression of an endogenous gene in said one or more cells;

(b) culturing said one or more cells under conditions favoring expression of said activated gene, thereby producing a gene product of said activated gene;

(c) screening said one or more cells for a cell in which a desired gene is activated or for a cell in which a desired phenotype is induced by said activated gene;

(d) treating said cell, in which said desired gene is activated or in which said desired phenotype is induced, with one or more test compounds to be screened for drug activity; and

(e) determining the ability of said one or more test compounds to interact with a product of said desired activated gene or to affect said desired phenotype.

PROPOSED CLAIMS
U.S. SERIAL NO. 09/484,331
(ATTORNEY DOCKET NO. 0221-0003L)

Claims 1-61 (cancelled).

Claim 62 (currently amended) A method for drug discovery comprising:

(a) integrating a vector comprising a transcriptional regulatory sequence into the genome of one or more eukaryotic cells, wherein said vector integration activates expression of an endogenous gene, by means of said transcriptional regulatory sequence, in said one or more cells;

(b) culturing said one or more cells under conditions favoring expression of said activated gene, thereby producing a gene product of said activated gene;

(c) screening said one or more cells from step (b) for a cell in which a desired gene is activated or for a cell in which a desired phenotype is induced by said activated gene;

(d) treating said cell, in which said desired gene is activated or in which said desired phenotype is induced, with one or more test compounds; and

(e) determining the ability of said one or more test compounds to interact with a product of said desired activated gene.

Claim 63 (currently canceled): A method for drug discovery comprising:

(a) integrating a vector into the genome of one or more eukaryotic cells, wherein said vector integration activates expression of an endogenous gene in said one or more cells;

(b) culturing said one or more cells in reduced-serum cell culture medium under conditions favoring production of a protein encoded by said activated gene and secretion of said protein into the cell culture medium;

(c) screening said one or more cells for a cell in which a desired gene is activated and the protein encoded by said desired gene is secreted into the cell culture medium; and

(d) screening one or more test compounds for drug activity by determining the ability of said test compounds to interact with said secreted protein in said cell culture medium.

Clam 64 (currently canceled):The method of claim 63, further comprising concentrating said cell culture medium prior to said screening in (d).

Claim 65 (currently canceled): The method of claim 63, further comprising isolating said protein prior to said screening in (d).

Claim 66 (currently canceled): The method of claim 62 wherein said vector comprises a transcriptional regulatory sequence and wherein expression of said endogenous gene is activated by means of said transcriptional regulatory sequence.

Claim 67 (currently canceled): The method of claim 63 wherein said vector comprises a transcriptional regulatory sequence and wherein expression of said endogenous gene is activated by means of said transcriptional regulatory sequence.

Claim 68 (currently amended): The method of claim 62 wherein said vector integrates into the genome by non-homologous recombination.

Claim 69 (previously added): A method for drug discovery comprising:

(a) integrating a vector, comprising a promoter, into the genome of one or more eukaryotic cells, by non-homologous recombination, wherein said promoter activates expression of an endogenous gene in said one or more cells;

(b) culturing said one or more cells under conditions favoring expression of said activated gene, thereby producing a gene product of said activated gene;

(c) screening said one or more cells for a cell in which a desired gene is activated or for a cell in which a desired phenotype is induced by said activated gene;

(d) treating said cell, in which said desired gene is activated or in which said desired phenotype is induced, with one or more test compounds to be screened for drug activity; and

(e) determining the ability of said one or more test compounds to interact with a product of said desired activated gene or to affect said desired phenotype.

Claim 70 (currently added) The method of claim 62 or claim 69 wherein the gene product is protein, the protein is purified from the cell and the test compound is exposed to the purified protein.

APPENDIX A